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Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status



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ABSTRACT

Background: Many patients with asthma remain symptomatic despite treatment with inhaled corticosteroids (ICS) with or without long-acting β_2 -agonists (LABAs). Tiotropium add-on to ICS plus a LABA has been shown to improve lung function and reduce exacerbation risk in patients with symptomatic asthma.

Objective: To determine whether the efficacy of tiotropium add-on therapy is dependent on patients' baseline characteristics.

Methods: Two randomized, double-blind, parallel-group, twin trials (NCT00772538 and NCT00776984) of once-daily tiotropium RespiMat® 5 μ g add-on to ICS plus a LABA were performed in parallel in patients with severe symptomatic asthma. Exploratory subgroup analyses of peak forced expiratory volume in 1 s (FEV₁), trough FEV₁, time to first severe exacerbation, time to first episode of asthma worsening, and seven-question Asthma Control Questionnaire responder rate were performed to determine whether results were influenced by baseline characteristics.

Results: 912 patients were randomized: 456 received tiotropium and 456 received placebo. Tiotropium improved lung function, reduced the risk of asthma exacerbations and asthma worsening, and improved asthma symptom control, compared with placebo, independent of baseline characteristics including gender, age, body mass index, disease duration, age at asthma onset, and FEV₁ % predicted at screening and reversibility. **Conclusion:** Once-daily tiotropium 5 μ g compared with placebo improved lung function, reduced the risk of asthma exacerbations and asthma worsening, and improved asthma symptom control, independent of a broad range of baseline characteristics, as add-on to ICS plus LABAs in patients with severe symptomatic asthma.

Trial registry: ClinicalTrials.gov; numbers NCT00772538 and NCT00776984 URL: www.clinicaltrials.gov.

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Abbreviations: ACQ-7, seven-question Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, hazard ratio; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; NC, not calculated; OR, odds ratio; peak FEV_{1(0–3h)}}, peak forced expiratory volume in 1 s within 3 h after the administration of maintenance therapy and study drug; SD, standard deviation; TALC, Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid.

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1. Introduction

Despite treatment according to guidelines with inhaled corticosteroids (ICS) as monotherapy or in combination with long-acting β_2 -agonists (LABAs) [1], at least 40% of patients diagnosed with asthma remain symptomatic [2–4].

One option to improve asthma control in patients who remain symptomatic despite treatment with ICS, with or without a LABA, is the addition of another controller therapy [1]; the long-acting anticholinergic bronchodilator tiotropium has recently been incorporated into the Global Initiative for Asthma 2015 treatment strategy as an option for addition at steps 4 and 5 in adult patients with a history of exacerbations [1]. The clinical efficacy and safety of treatment with tiotropium as add-on to standard ICS maintenance treatment, with or without a LABA, have been demonstrated in several trials in adult patients across severities of symptomatic asthma [5–13].

In studies of patients with mild or moderate disease receiving maintenance treatment with ICS alone, tiotropium improved lung function and asthma control [5,7,8,10,11,13], and similar efficacy was confirmed in three studies comparing the efficacy of tiotropium with salmeterol as add-on to ICS [5,7,10]. In patients with more severe asthma – symptomatic despite treatment with ICS (≥ 800 μ g budesonide or equivalent) plus a LABA – a short-term trial demonstrated significant improvements in lung function following tiotropium add-on therapy [6]. Lastly, in a similar patient population, two large phase III, 48-week, randomized, double-blind, placebo-controlled studies with identical design (PrimoTina-asthma[®]) confirmed that tiotropium 5 μ g as add-on provides significant and sustained bronchodilation [9]. In these studies, tiotropium also reduced the risk of severe exacerbations and asthma worsening by 21% (hazard ratio: 0.79; $p = 0.03$) and 31% (hazard ratio: 0.69; $p < 0.001$), respectively [9]. Significant improvements in lung function and asthma symptom control were also observed with the 5 μ g dose in a phase III, 52-week study in Japanese patients with symptomatic asthma despite ICS with or without a LABA [12]. The long-term safety of tiotropium was found to be comparable with that of placebo [9,12].

Tiotropium has been shown to be efficacious across asthma severities, but it has yet to be determined whether there is a clinical phenotype or characteristic that predicts whether patients with asthma will respond favorably to the addition of this treatment. The purpose of the current analyses was to explore whether there are features that may be used to predict which patients might benefit from the introduction of tiotropium 5 μ g compared with placebo in terms of improvements in lung function and reduction in the risk of exacerbations or asthma worsening. We present subgroup analyses of data from the two phase III PrimoTina-asthma[®] studies performed in patients with severe symptomatic asthma despite treatment with ICS plus LABA therapy [9]. The potential predictive features examined included, among other characteristics, age, smoking status, forced expiratory volume in 1 s (FEV₁) reversibility, and allergic status. We also assessed whether the lung function benefits and reduction in the risk of exacerbations or asthma worsening translate into improved asthma symptom control and quality of life in the full patient population.

2. Methods

2.1. Study design

Two phase III, 48-week, randomized, double-blind, placebo-controlled, parallel-group, twin studies (PrimoTina-asthma[®]: NCT00772538 and NCT00776984) were conducted in parallel, using the same protocol, at 148 sites in 15 countries

between October 2008 and July 2011, to assess the efficacy and safety of tiotropium 5 μ g as add-on to ICS plus LABA maintenance therapy in symptomatic patients with severe persistent asthma. The trials were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice, and all participating patients provided written, informed consent. Full details of the study design and main results have been published previously [9].

2.2. Patients

The trials included patients who were aged 18–75 years with a ≥ 5 -year history of asthma at study enrollment and initial diagnosis before the age of 40 years, and who were currently symptomatic as defined by a seven-question Asthma Control Questionnaire (ACQ-7) mean score of ≥ 1.5 [14]. Eligible patients also had moderate or severe persistent airflow limitation, defined as post-bronchodilator FEV₁ $\leq 80\%$ of predicted normal and $\leq 70\%$ of the forced vital capacity measured 30 min after inhaling four puffs of 100 μ g salbutamol (albuterol) at their initial screening visit. All patients had been receiving daily treatment with both ICS (≥ 800 μ g budesonide or equivalent dose of another ICS) and a LABA for at least 4 weeks before screening. Patients must also have experienced at least one exacerbation requiring treatment with systemic glucocorticoids in the previous year and either never to have smoked or to have smoked for less than 10 pack-years with no smoking in the year before enrollment.

The main exclusion criteria were chronic obstructive pulmonary disease, serious unstable co-existing illnesses, and an asthma exacerbation or respiratory tract infection within 4 weeks before enrollment. Full details of inclusion and exclusion criteria have been published previously [9].

2.3. Study treatments

Following a 4-week screening period, patients were randomized in a 1:1 ratio to once-daily tiotropium 5 μ g (two puffs of 2.5 μ g) or matching placebo in the morning, both via the Respimat[®] Soft Mist[™] inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany), as add-on therapy to their existing ICS (≥ 800 μ g budesonide or equivalent dose) plus LABA treatment regimen, which continued unaltered.

The use of other maintenance therapies during the study, such as theophylline, leukotriene receptor antagonists (LTRAs), anti-immunoglobulin E (IgE) antibody, or oral glucocorticoids (≤ 5 mg/day), was allowed provided the dose had been stable for ≥ 4 weeks before study entry and remained unaltered. In addition, systemic steroids were permitted for the treatment of severe asthma exacerbations [9]. Open-label, metered-dose inhalers of salbutamol were provided as rescue medication.

2.4. Assessments

Patients attended study clinics for assessment on 10 occasions during the trials: an initial screening visit (Visit 1, Week –4); at randomization to study treatment (Visit 2, baseline, Week 0); at Weeks 4 and 8; and then every 8 weeks until Week 48 (Visit 9, end of treatment). A follow-up visit at Week 52 was scheduled to record adverse events and concomitant therapies. During these visits, patients underwent lung function tests, completed the ACQ-7 and Asthma Quality of Life Questionnaire (AQLQ), and were questioned about exacerbations and adverse events.

2.5. Study endpoints

For each trial, the co-primary endpoints included peak FEV₁

response within 3 h after the administration of maintenance therapy and study drug (peak $FEV_{1(0-3h)}$) and trough FEV_1 response, measured at the end of the dosing interval (24 h after drug administration), 10 min before the next dose, at Week 24 [9]. A third pre-specified co-primary endpoint, evaluated from the 48-week pooled data, was time to the first severe asthma exacerbation, defined as a deterioration of asthma necessitating initiation, or at least a doubling, of systemic glucocorticoids for ≥ 3 days [9,15].

Secondary endpoints (pooled data) included time to the first episode of asthma worsening, defined as at least one asthma symptom outside the patient's usual range that lasted for ≥ 2 consecutive days and/or a decrease in the patient's best morning peak expiratory flow $\geq 30\%$ from their mean morning peak expiratory flow for ≥ 2 consecutive days [9].

Analyses of both pre-planned and *post hoc* subgroups of pooled study data were performed to determine whether lung function results at Week 24, time to first severe exacerbation and first episode of asthma worsening over 48 weeks, and asthma control at Weeks 24 and 48 with tiotropium 5 μ g add-on therapy varied according to patients' baseline characteristics. The pre-planned subgroups included: gender; body mass index; FEV_1 % predicted at screening; FEV_1 reversibility (following 400 μ g salbutamol); allergic status by clinician judgment, serum IgE, or blood eosinophils; B16 combination genotype in the coding region of the β_2 -adrenergic receptor gene (only in patients who consented to participate in the pharmacogenetics portion of the trials); and country/region. In addition, *post hoc* subgroups were defined for the assessment of the efficacy of treatment according to patients' age, disease duration, age at asthma onset, smoking status, LTRA use at baseline, race, and ethnicity. The subgroups were chosen on the basis that patients with or without these disease or demographic characteristics might exhibit differing levels of response to tiotropium 5 μ g add-on therapy. The thresholds used to define the subgroups and corresponding rationales are presented in Table S1.

Overall pooled analyses of ACQ-7 responder rates at Weeks 24 and 48 are also presented to allow for comparison with other phase III trials in which ACQ-7 responder rate was an endpoint. Lastly, pooled analyses of AQLQ responder rate at Weeks 24 and 48 were performed. A response was defined as a change in ACQ-7 or AQLQ score from study baseline of ≥ 0.5 , the minimal clinically important difference [16,17].

2.6. Statistical analyses

Univariate subgroup analyses were performed using subgroup-restricted regression analyses (i.e. analyses within subgroups): mixed-model repeated measures for peak $FEV_{1(0-3h)}$ and trough FEV_1 ; Cox regression for time to first severe exacerbation and time to first episode of asthma worsening; and logistic regression for ACQ-7 responder rate. Additional testing for interactions was performed by introducing "subgroup" and "subgroup-by-treatment-interaction" terms into the analysis models. Subgroup analyses were largely pre-specified in the protocol (see 2.5 Study endpoints); however, the study was not powered to detect and exclude possible effects and interactions, and no statistical correction was made for multiplicity; all subgroup analyses should therefore be interpreted as exploratory in nature. For all subgroup analyses, a nominal interaction p value ≤ 0.05 was regarded as indicative that the treatment effect was potentially different across subgroup categories.

Overall ACQ-7 and AQLQ responder analyses were conducted by Wilcoxon test to determine the percentage of patients with the minimal clinically important difference in score of ≥ 0.5 [16,17]. Net response rate was calculated as the difference between response

and worsening [18].

All efficacy analyses were performed on the full analysis set, defined as all patients who underwent randomization and received at least one dose of a study drug and had at least one on-treatment efficacy measurement. For longitudinal analyses, the mixed-model repeated measures model accounts for missing data throughout the course of the trial; for time-to-event analyses, patient drop-outs are incorporated in the Cox regression analyses.

3. Results

3.1. Baseline demographics

Across the two studies, 912 patients were randomized to study treatment. Of these, 409 patients receiving tiotropium 5 μ g and 405 patients receiving placebo completed the trials. Patients' baseline characteristics were similar across the two treatment groups (Table 1) [9]. The majority of patients were female (60.4%), and the mean age was 53.0 years. The mean duration of asthma was 30.3 years, most patients had never smoked (75.9%), and there were no current smokers; ex-smokers had a mean smoking history of 5.1 pack-years.

3.2. Efficacy

Subgroup analyses demonstrated that, at Week 24, improvements in both peak $FEV_{1(0-3h)}$ (Fig. 1) and trough FEV_1 (Fig. S1) with tiotropium 5 μ g compared with placebo were independent of all patient baseline characteristics assessed: gender; age; body mass index; disease duration; age at asthma onset; smoking status; FEV_1 % predicted at screening; FEV_1 reversibility; LTRA use at baseline; allergic status by clinician judgment, serum IgE, or blood eosinophils; B16 genotype combination; race; ethnicity; and country/region. However, the trough FEV_1 improvements were of borderline statistical significance in the smoking status subgroup ($p = 0.052$).

The increases in time to first severe exacerbation (Fig. 2) and first episode of asthma worsening (Fig. 3) with tiotropium 5 μ g compared with placebo over the 48-week treatment period were also not significantly influenced by any of the patient baseline characteristics assessed. A trend for improvement was observed in patients with LTRA use at baseline, but did not reach statistical significance.

In an analysis of overall ACQ-7 responder rate data, a statistically significant improvement in asthma symptom control was observed in patients treated with tiotropium 5 μ g compared with placebo after both 24 and 48 weeks (Fig. 4). At Week 24, 53.9% of patients who received tiotropium 5 μ g were responders compared with 46.9% of patients who received placebo (odds ratio [OR]: 1.32; 95% confidence interval [CI]: 1.01–1.73; $p = 0.04$). The difference in responder rate between tiotropium 5 μ g and placebo increased at Week 48 (OR: 1.68; 95% CI: 1.28–2.21; $p < 0.001$). Similar results were observed in *post hoc* analyses of five-question and six-question ACQ responder rates (see Table S2). The improvements in ACQ-7 responder rate with tiotropium 5 μ g compared with placebo were not significantly influenced by patients' baseline characteristics, except for smoking status and FEV_1 % predicted at screening at Week 24 (Fig. S2A) and blood eosinophils at Week 48 (Fig. S2B).

An analysis of AQLQ responder rate data showed numerically greater but nonsignificant improvements with tiotropium 5 μ g versus placebo, with a numerically larger improvement also observed at Week 48 (OR: 1.20; 95% CI: 0.92–1.57; $p = 0.19$) compared with Week 24 (OR: 1.12; 95% CI: 0.85–1.47; $p = 0.44$) (Fig. S3).

Table 1
Baseline demographics and disease characteristics.

	Tiotropium 5 µg (n = 456)	Placebo (n = 456)	Total (N = 912)
Gender, n (%)			
Male	183 (40.1)	178 (39.0)	361 (39.6)
Female	273 (59.9)	278 (61.0)	551 (60.4)
Age (years), mean ± SD	52.2 ± 12.5	53.8 ± 12.2	53.0 ± 12.4
Body mass index (kg/m ²), mean ± SD	28.2 ± 5.9	28.2 ± 6.1	28.2 ± 6.0
Race, n (%)			
White	376 (82.5)	383 (84.0)	759 (83.2)
Black	22 (4.8)	25 (5.5)	47 (5.2)
Asian	56 (12.3)	47 (10.3)	103 (11.3)
Other	2 (0.4)	1 (0.2)	3 (0.3)
Smoking status, n (%)			
Never smoked	340 (74.6)	352 (77.2)	692 (75.9)
Ex-smoker	116 (25.4)	104 (22.8)	220 (24.1)
Smoking history (pack-years), mean ± SD	5.4 ± 2.8	4.8 ± 2.7	5.1 ± 2.7
Concomitant treatment, n (%) ^a			
Inhaled corticosteroids	452 (99.1)	449 (98.5)	901 (98.8)
Long-acting β ₂ -agonists	442 (96.9)	444 (97.4)	886 (97.1)
Leukotriene receptor antagonists	96 (21.1)	107 (23.5)	203 (22.3)
Oral glucocorticoids	75 (16.4)	79 (17.3)	154 (16.9)
Theophylline	75 (16.4)	77 (16.9)	152 (16.7)
Antihistamines	79 (17.3)	55 (12.1)	134 (14.7)
Short-acting anticholinergics	34 (7.5)	33 (7.2)	67 (7.3)
Omalizumab	12 (2.6)	24 (5.3)	36 (3.9)
Long-acting anticholinergics	13 (2.9)	11 (2.4)	24 (2.6)
Age at asthma onset (years), mean ± SD ^b	22.6 ± 12.8	22.7 ± 13.0	22.7 ± 12.9
Duration of asthma (years), mean ± SD ^b	29.6 ± 13.6	31.0 ± 14.1	30.3 ± 13.9
ACQ-7 score ^c , mean ± SD	2.6 ± 0.7	2.6 ± 0.7	2.6 ± 0.7
AQLQ score ^d , mean ± SD	4.6 ± 1.0	4.6 ± 1.1	4.6 ± 1.1
FEV ₁ % predicted, mean ± SD ^e	55.9 ± 13.1	56.0 ± 13.2	56.0 ± 13.1
FVC % predicted, mean ± SD ^e	79.9 ± 17.3	80.5 ± 16.8	80.2 ± 17.0
FEV ₁ /FVC (%), mean ± SD ^e	58.7 ± 10.3	58.1 ± 10.0	58.4 ± 10.1

Treated set.

ACQ-7: seven-question Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, FEV₁: forced expiratory volume in 1 s, FVC: forced vital capacity, SD: standard deviation.^a Received within 3 months before screening (Visit 1).^b Measured at screening (Visit 1).^c ACQ-7 consists of seven questions which are scored on a scale of 0 (no impairment) to 6 (maximum impairment).^d AQLQ consists of 32 questions which are scored on a scale of 1 (severely impaired) to 7 (no impairment).^e Pre-bronchodilator, measured at randomization (Visit 2).

4. Discussion

The subgroup analyses presented here of data from two large phase III studies indicate that tiotropium 5 µg as add-on to ICS plus a LABA improves lung function, reduces the risk of exacerbations and asthma worsening, and improves asthma symptom control, independent of a broad range of baseline characteristics in adult patients with severe symptomatic asthma despite ICS plus LABA therapy.

Our data show that the presence or magnitude of lung function response, risk of exacerbations and asthma worsening following tiotropium, when administered as add-on to ICS plus a LABA, did not appear to be influenced by baseline characteristics, including: gender; age; body mass index; disease duration; age at asthma onset; smoking status; FEV₁ reversibility; LTRA use at baseline; B16 genotype combination; race; ethnicity; and country/region. Responses were also shown to be independent of patients' allergic status by clinician judgment, serum IgE, or blood eosinophils, which is supported by recently presented analyses of data from these trials which did not show any interaction between risk of exacerbations or asthma worsening over the range of IgE (2–2000 µg/L) or blood eosinophil (0.05–7.00 × 10⁹/L) levels [19–23]. With the exception of smoking status and FEV₁ % predicted at Week 24 and blood eosinophils at Week 48, improvements in ACQ-7 responder rate were also found to be independent of patients' baseline characteristics.

Our results, however, should not be viewed as confirmatory for

several reasons. First, this is a *post hoc* subgroup analysis, and the study was not powered for such analyses. Secondly, the creation of subgroup categories increases the variation of results within subgroups and the likelihood of spurious significant interactions. Further, we made no statistical correction for multiplicity, and such correction would have left no significant interactions.

Nevertheless, two interactions deserve further discussion. A numerically greater benefit following the addition of once-daily tiotropium was observed in ex-smokers across all endpoints when compared with patients who had never smoked, with the differences in trough FEV₁ response almost reaching statistical significance. The reason for this observation, which applied to ex-smokers who had not smoked for a year or more and with a limited smoking history of only 5.1 pack-years, is unclear. The trends for improvement in time to first severe exacerbation and first episode of asthma worsening that were observed for patients with LTRA use at baseline who were treated with tiotropium were not observed for measures of FEV₁ or ACQ-7 responder rate, and are therefore likely to be a spurious effect.

Previous studies have suggested that responsiveness to short-acting anticholinergics in asthma increases with age, degree of airflow obstruction, and duration of disease [24–26]. Our findings in relation to the long-acting anticholinergic tiotropium agree broadly with those of Peters et al. [27] from the “Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid” (TALC) study of tiotropium 18 µg (via Spiriva®

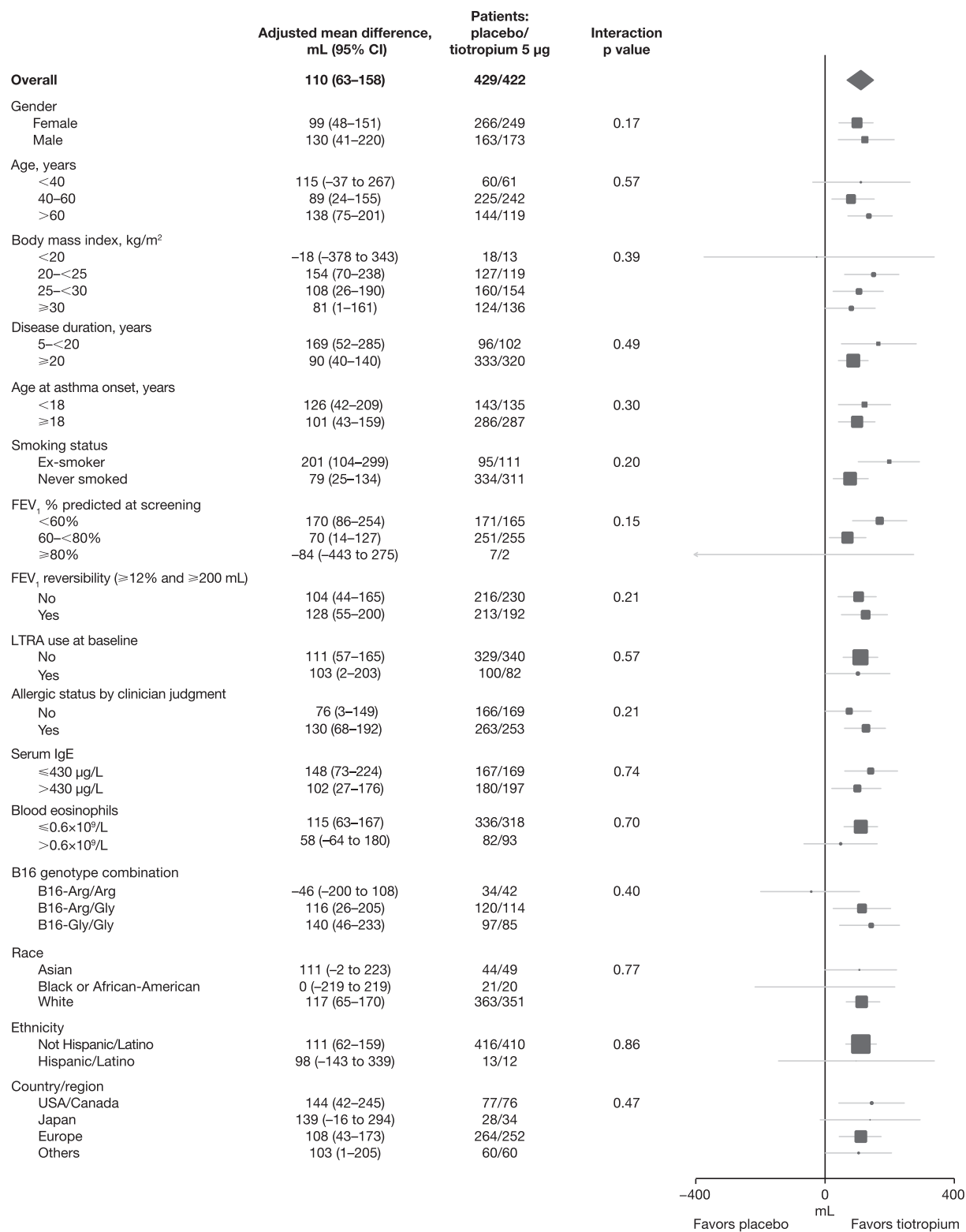


Fig. 1. Peak FEV_{1(0–3h)} at Week 24 by baseline characteristics. Full analysis set. CI: confidence interval, FEV₁: forced expiratory volume in 1 s, IgE: immunoglobulin E, LTRA: leukotriene receptor antagonist, peak FEV_{1(0–3h)}: peak forced expiratory volume in 1 s within 3 h after the administration of maintenance therapy and study drug.

HandiHaler®; Boehringer Ingelheim) performed in patients with asthma inadequately controlled on ICS maintenance therapy. However, unlike in the TALC study, neither the degree of airflow limitation nor the presence or absence of FEV₁ reversibility in response to a short-acting β₂-agonist were found to be associated

with a positive response in the present analysis. Our findings are also broadly in agreement with those from the recent “Blacks and Exacerbations on LABA vs Tiotropium” study [28] in which B16–Arg/Gly polymorphisms were not associated with significant differences in time to first exacerbation, mean number of exacerbations,

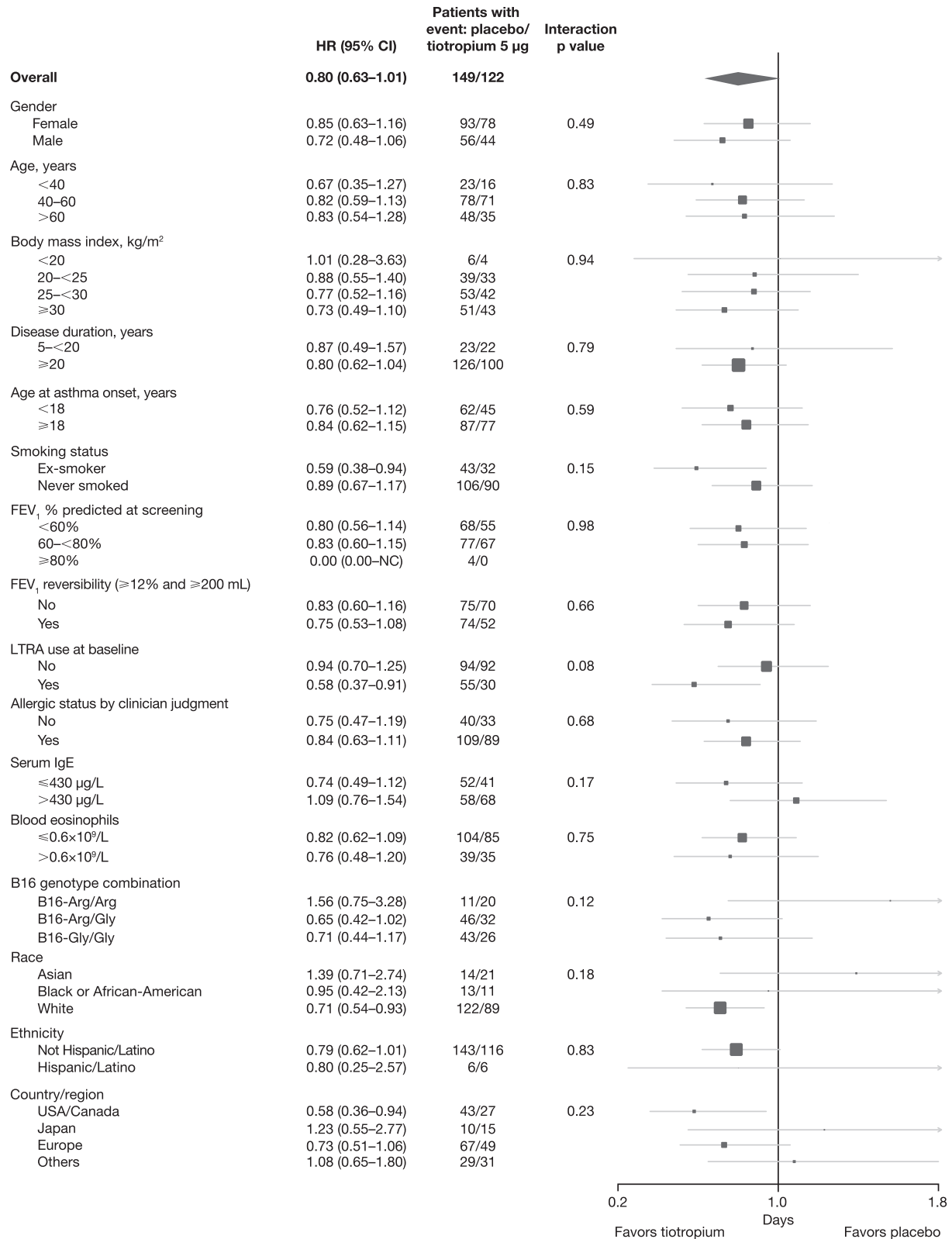


Fig. 2. Time to first severe asthma exacerbation over 48 weeks by baseline characteristics. Full analysis set. CI: confidence interval, FEV₁: forced expiratory volume in 1 s, HR: hazard ratio, IgE: immunoglobulin E, LTRA: leukotriene receptor antagonist, NC: not calculated.

or lung function following tiotropium plus ICS therapy, compared with LABA plus ICS, in black adults with asthma.

In the original publication of individual trial data from the PrimoTinA-asthma[®] trials, the mean changes in ACQ-7 and AQLQ

scores, compared with placebo, were modest and statistically significant at Week 24 in only one of the two trials [9]. Positive responder rates or net treatment benefit analyses provide a more clinically useful assessment of results for analyses in which the

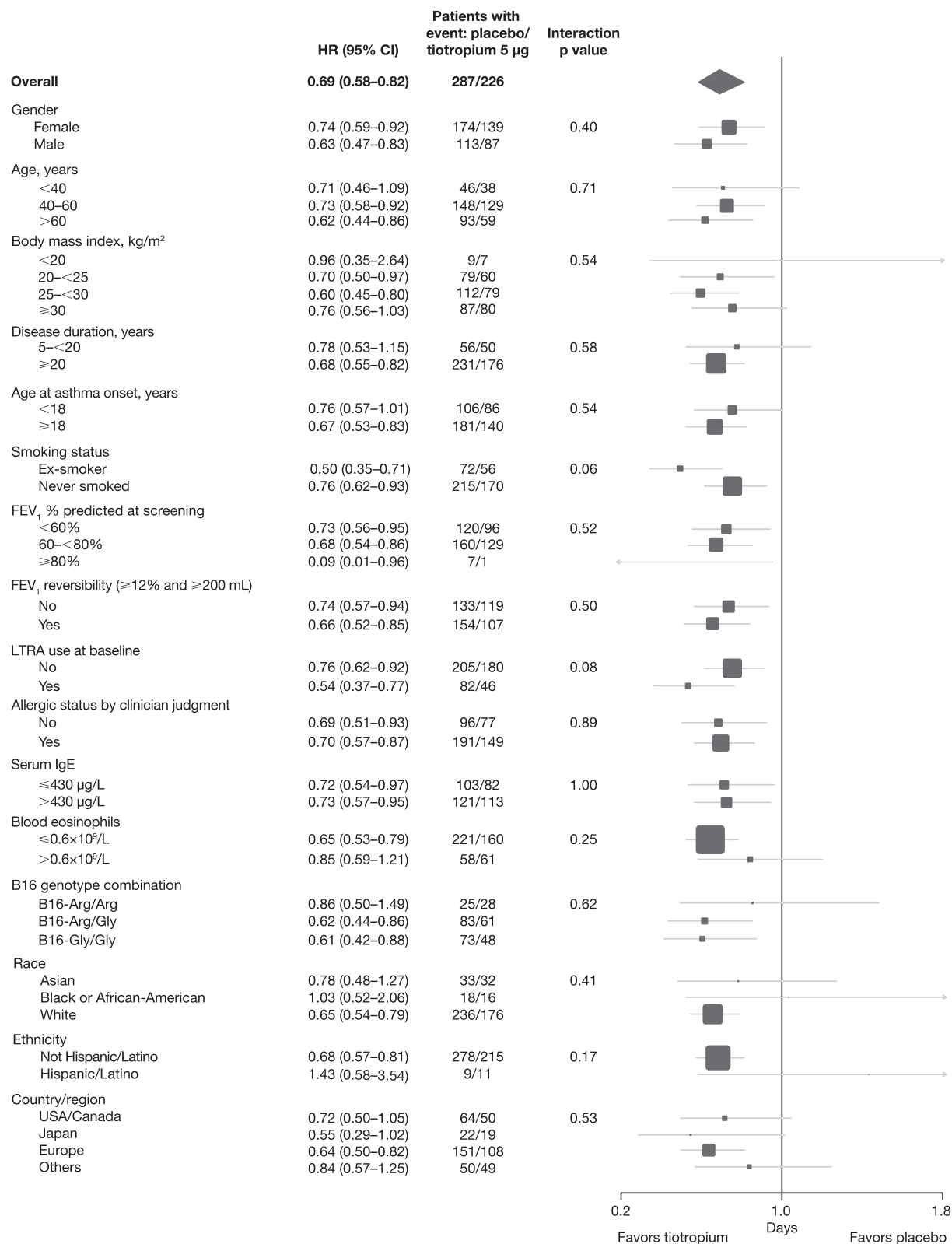


Fig. 3. Time to first episode of asthma worsening over 48 weeks by baseline characteristics. Full analysis set. CI: confidence interval, FEV₁: forced expiratory volume in 1 s, HR: hazard ratio, IgE: immunoglobulin E, LTRA: leukotriene receptor antagonist.

achievement of a minimal clinically important difference indicates an individual's improvement [18,29]. In whatever way assessed, all such comparisons are influenced by the large placebo effect seen in these and other studies for these endpoints, presumed to relate to

improved adherence in the clinical trial environment. In the present pooled ACQ-7 responder rate analyses, a response was defined as the minimal clinically important difference (i.e. a decrease in ACQ-7 score from study baseline of ≥0.5) [16]. The addition of

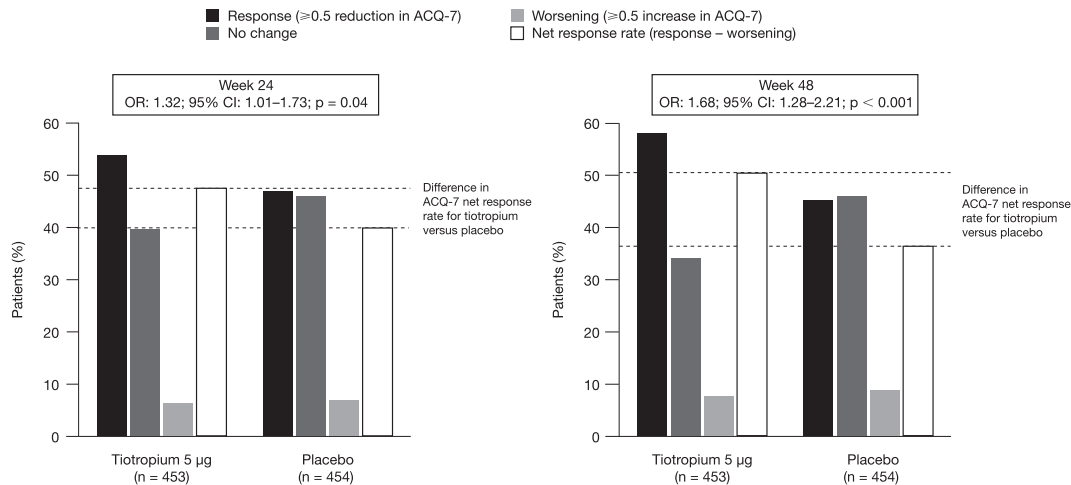


Fig. 4. ACQ-7 responder rate at Weeks 24 and 48. Full analysis set. ACQ-7: seven-question Asthma Control Questionnaire, CI: confidence interval, OR: odds ratio.

tiotropium 5 µg was found to significantly improve asthma symptom control at Weeks 24 and 48 compared with placebo. Improvements in asthma symptom control with the addition of tiotropium have also been observed in studies of patients with moderate symptomatic asthma receiving only ICS maintenance therapy (5 µg, OR: 1.32; 95% CI: 1.02–1.71; $p = 0.04$; 2.5 µg, OR: 1.33; 95% CI: 1.03–1.72; $p = 0.03$) [10]. AQLQ responder rates (where a response was defined as an increase in AQLQ score from a study baseline of ≥ 0.5) [17] were high in both the active and placebo treatment arms. Although there was a trend toward improvement in AQLQ responder rate over time with tiotropium 5 µg compared with placebo, this was not significant, suggesting that measures of asthma control and quality of life assess different aspects of patients' perceptions of asthma.

The beneficial effects of tiotropium seen in these trials need to be viewed within the context of the patient population studied. All patients were symptomatic and at risk of exacerbations despite their current treatment with ICS plus a LABA. Alternative treatments at this step are limited and vary in terms of efficacy, safety, and/or availability. There is limited evidence that theophylline and LTRAs improve asthma control or reduce exacerbations when added to ICS plus LABA treatment [30,31], and systemic glucocorticoids are associated with marked side effects [32]. Omalizumab is indicated only for patients with specific features of allergic asthma, and its use is further limited by cost [33]. Importantly, the safety and tolerability of tiotropium 5 µg were found to be comparable with those of placebo when added to ICS plus LABA maintenance therapy [9], and the findings from our current analyses suggest that tiotropium is effective across a broad range of patient characteristics. Studies involving more detailed phenotyping across different severities of asthma and studies including biomarkers may be helpful in further defining patients with a favorable response to tiotropium.

In summary, the results of these subgroup analyses suggest that once-daily tiotropium 5 µg as add-on to ICS plus a LABA may provide a beneficial treatment option for patients with severe asthma who remain symptomatic despite ICS plus a LABA, regardless of baseline clinical features.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.06.013>.

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